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Appl. No. 10/016,850

REQUEST FOR CONTINUED EXAMINATION AND SUBMISSION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 10/016,850 Confirmation No. 7435
Applicant : HUGHES et al.
Filed : December 14, 2001
Title : PHARMACEUTICAL CONJUGATES WITH ENHANCED
PHARMACOKINETIC CHARACTERISTICS

TC/A.U. : 1600/1618
Examiner : FAY, Z.

Docket No. : D-3004
Customer No. : 33197

Mail Stop: Appeal Brief

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Carlos A. Fisher
Stout, Uxa, Buyan & Mullins LLP

For Appellant

06/12/2008 LTRUONG 00000029 10016850

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Fees Pursuant to the Consolidated Appropriations Act 2005 (H.R. 4818).

FEE TRANSMITTAL For FY 2008

Patent fees are subject to annual revision.

☐ Application claims small entity status. See 37 CFR 1.27TOTAL AMOUNT OF PAYMENT (\$)
510

Complete if Known

Application Number	10/016,850
Filing Date	12/14/2001
First Named Inventor	Hughes
Examiner Name	Fay, Z.
Art Unit	1618
Attorney Docket No.	D-3004

METHOD OF PAYMENT (check all that apply)

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES		SEARCH FEES		EXAMINATION FEES		Fees Paid (\$)
	Fee (\$)	Small Entity Fee (\$)	Fee (\$)	Small Entity Fee (\$)	Fee (\$)	Small Entity Fee (\$)	
Utility	310	155	510	255	210	105	
Design	210	105	100	50	130	65	
Plant	210	105	310	155	160	80	
Reissue	310	155	510	255	620	310	
Provisional	210	105	0	0	0	0	
Subtotal (1)						0	

2. EXCESS CLAIM FEES

Fee Description	Fee (\$)	Small Entity Fee (\$)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	210	105
Multiple Dependent Claims	370	185
Total Claims	Extra Claims	Fee (\$)
-20 or HP =	x	
HP = highest number of total claims paid for, if greater than 20		
Indep. Claims	Extra Claims	Fee (\$)
-3 or HP =	x	
HP = highest number of independent claims paid for, if greater than 3		
Subtotal (2)		0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$260 (\$130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee (\$)	Fee Paid (\$)
-100 =	/50=	(round up to a whole number)	x	
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- ☐ Surcharge - Late filing fee or oath/declaration: \$130 fee (\$65 small entity discount)
- ☐ Non-English Specification: \$130 fee (no small entity discount)
- ☐ 1-month extension of time: \$120 fee (\$60 small entity discount)
- ☐ 2-month extension of time: \$460 fee (\$230 small entity discount)
- ☐ 3-month extension of time: \$1050 fee (\$525 small entity discount)
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- ☐ Information Disclosure Statement Fee: \$180 fee (no small entity discount)
- ☐ Notice of Appeal: \$510 fee (\$255 small entity discount)
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- ☐ Request for Oral Hearing: \$1030 fee (\$515 small entity discount)
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Subtotal (4) 510

SUBMITTED BY

Name (Print/Type)	Carlos A. Fisher	Registration No. (Attorney/Agent)	36,510	Telephone	949-450-1750
Signature				Date	6/9/08

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FEE TRANSMITTAL
For FY 2008

Patent fees are subject to annual revision.

☐ Application claims small entity status. See 37 CFR 1.27**TOTAL AMOUNT OF PAYMENT** (\$) 510**Complete if Known**

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-100 = _____	/50= _____	(round up to a whole number)	x _____	= _____
Subtotal (3)				0

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<input type="checkbox"/> Surcharge - Late filing fee or oath/declaration: \$130 fee (\$65 small entity discount)	
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<input checked="" type="checkbox"/> Filing a Brief in Support of Appeal: \$510 fee (\$255 small entity discount)	510
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<input type="checkbox"/> Other: _____	
Subtotal (4)	510

SUBMITTED BY

Name (Print/Type)	Carlos A. Fisher	Registration No. (Attorney/Agent)	36,510	Telephone	949-450-1750
Signature				Date	6/9/08



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No. : 11/016,850
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Customer No. : 33197

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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| <input checked="" type="checkbox"/> Reply Brief | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> Stamped, self-addressed postcard | <input type="checkbox"/> |
| <input checked="" type="checkbox"/> Check for \$515 | <input type="checkbox"/> Other: _____ |

Each of the 4 above-identified documents are enclosed herewith.

Date: June 9, 2008

Respectfully submitted,



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REAL PARTY IN INTEREST

The inventors, Patrick M. Hughes and Orest Olejnik, each assigned their entire interest in this patent application to Allergan Sales, Inc. via an assignment document executed on December 10, 2001 and recorded with the United States Patent and Trademark Office at reel 023899, frame 0630. Allergan Sales, Inc. was subsequently merged with Allergan Sales, L.L.C. Allergan Sales, L.L.C. then assigned its entire interest in this application to Allergan, Inc.

Allergan, Inc. is therefore the owner of this patent application and the real party in interest in this appeal.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF CLAIMS

Claims 7 and 10 have been withdrawn from prosecution.

Claims 13, and 17-23 have been cancelled without prejudice to their possible later presentation in a continuation or divisional application.

Claims 1-6, 8, 9, 11, 12, 14-16 and 24-26 are currently pending and have been rejected and are under appeal.

STATUS OF AMENDMENTS

No amendments have been made since the mailing date of the Office Action of July 13, 2006.

SUMMARY OF CLAIMED SUBJECT MATTER

Claim 1 is drawn to a topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate, wherein the carrier comprises an ophthalmically useful therapeutic component (TC) covalently coupled in a specific manner to an efficacy enhancing component (EEC) effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye. The efficacy-enhancing component comprises a specifically recited generic chemical structure. This claim is supported by the specification at, e.g., pages 2-3.

Claim 2 is drawn to the composition of claim 1 in which the TC and EEC are joined directly by a covalent bond and the carrier comprises a liquid. Support for this claim is as indicated for claim 1; in addition, support can be found at page 3, lines 21 and 22 and page 17, lines 9-11.

Claim 3 is drawn to the composition of claim 1 in which the TC and EEC are joined by a linker. Support for this claim is as indicated for claim 1; in addition, support can be found at page 3, lines 22-24.

Claim 4 is drawn to the composition of claim 1 wherein R1 and R2 are H and R3 is a linker. Support for this claim is as indicated for claim 1; in addition, support can be found at page 12, lines 22 and 23.

Claim 5 is drawn to the composition of claim 1 wherein the efficacy enhancing component is a memantine. Support for this

claim is as indicated for claim 1; in addition, support can be found at page 12, lines 23 and 24.

Claim 6 is drawn to the composition of claim 1 wherein the linker is selected from a specifically indicated Markush group of linkers. Support for this claim is as indicated for claim 1; in addition, support can be found at page 4.

Claim 8 is drawn to the composition of claim 1 wherein the therapeutic component is selected from the group consisting of quinoxaline, (2-imidazolyl-2-ylamino) quinoxaline, 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline, and mixtures thereof. Support for this claim is as indicated for claim 1; in addition, support can be found at page 9, line 31 to page 10, line 3.

Claim 9 is drawn to the composition of claim 1 wherein the efficacy-enhancing component comprises a memantine, and the conjugate further comprises a linker covalently joining the therapeutic component and the memantine in a specific manner. Support for this claim is as indicated for claim 1; in addition, support can be found at page 12, lines 23 and 24 and page 3, lines 22-24.

Claim 11 is drawn to the composition of claim 8 wherein the efficacy-enhancing component comprises a memantine, and the conjugate further comprises a linker joining the therapeutic component and the memantine. Support for this claim is as indicated for claim 8; in addition, support can be found at page 12, lines 23 and 24 and page 3, lines 22-24 and page 14, lines 32-34.

Claim 12 is drawn to the composition of claim 1 wherein the therapeutic component and the efficacy enhancing component disassociate under physiological conditions. Support for this claim is as indicated for claim 1; in addition, support can be found at page 14, lines 4-6.

Claim 14 is drawn to the composition of claim 1 wherein the conjugate has an aqueous solubility, a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component which is not joined to an efficacy enhancing component. Support for this claim is as indicated for claim 1; in addition, support can be found at page 11, lines 3-7 and Example 6.

Claim 15 is drawn to the composition of claim 1 wherein the conjugate is a salt. Support for this claim is as indicated for claim 1; in addition, support can be found at page 11, line 15-28.

Claim 16 is drawn to a topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate, wherein the carrier comprises an ophthalmically useful therapeutic component (TC) covalently coupled via a linker to an efficacy enhancing component (EEC) effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye. The efficacy-enhancing component comprises a specifically recited generic chemical structure, as is the linker. This claim is supported by the specification at, e.g., pages 2-4.

Claim 24 is drawn to a topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate, wherein the carrier comprises an ophthalmically useful therapeutic component (TC), comprising a ophthalmically useful quinoxoline component, covalently coupled via a linker to an efficacy enhancing component (EEC) effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye. The efficacy-enhancing component and linker each comprise specifically recited generic chemical structures. This claim is supported by the specification at, e.g., pages 2-4 and page 9, line 31 to page 10, line 3.

Claim 25 is drawn to the composition of claim 24 wherein the therapeutic component is selected from the group consisting of quinoxaline, (2-imidazolyl-2-ylamino) quinoxaline, 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline, and mixtures thereof. This claim is supported by the specification at, e.g., pages 2-4 and page 9, line 31 to page 10, line 3.

Claim 26 is drawn to the composition of claim 25 wherein the therapeutic component comprises brimonidine tartrate. Support for this claim is as indicated for claim 25 and at page 17, line 32.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

Pending claims 1-6, 8, 9, 11, 12, 14-16 and 24-26 have been rejected as allegedly unpatentable under 35 U.S.C. § 103(a) over the combination of DeSantis (U.S. Patent Publication 2001/0047012) and Collins et al., (WO 01/92288).

ARGUMENT

I. Rejections Pursuant to 35 U.S.C. §103(a)

A) Did the Examiner err by finding that claims 1-6, 8, 9, 11, 12, 14-16 and 24-26 are obvious over Desantis (U.S. Patent Publication 2001/0047012) and Collins et al., (WO 01/92288)?

i) Claims 1-6, 8, 9, 11, 12, and 14-16.

a) Did the examiner err by finding that the presently claimed topical ophthalmic composition containing a single conjugated therapeutic molecule targeted to the posterior segment of the eye are prima facie obvious over DeSantis, which describes treating glaucoma and elevated IOP with a combination of an anterior segment-acting IOP-lowering agent and a glutamate antagonist, and Collins, which discloses conjugates comprising antibiotic agents targeted to non-ocular infectious tissue.

1) The combination of DeSantis and Collins fail to establish a *prima facie* case of obviousness over the present invention, since the prior art fails to provide a reason for the inventors' choices in conceiving the present invention.

A patent claim is in violation of 35 U.S.C. §103(a) if the difference between the teachings of the prior art and of the claimed invention when taken as a whole are such that a person of ordinary skill in the art would find the claimed invention obvious in light of the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (S.Ct. 1966).

The present invention is directed to a topical ophthalmic composition comprising a conjugated molecule comprising an EEC

and a TC. Upon topical instillation of the ophthalmic composition, the EEC not only increases the partition coefficient of the TC, but is believed to bind the retinal epithelium, thereby selectively targeting the TC to the retina. See e.g., *Specification*, page 11, lines 3-28.

DeSantis et al. discuss various combinations of a) a glutamate antagonist and b) an IOP (intraocular pressure) controlling agent for the treatment of glaucoma or ocular hypertension. The list of glutamate antagonists includes 6 very broad generic structures, and all isomers and pharmaceutically acceptable salts thereof (these generic structures do not include amantidines), reference to additional compounds listed in a PCT application (WO 94/13275), and a list of 14 additional compounds. The number of glutamate antagonists listed in DeSantis et al., thus number in the thousands. One of the 14 additional compounds is memantine. See DeSantis et al., page 2, paragraphs [0009] through [0018].

Likewise, DeSantis discloses that "the IOP-lowering agents useful in the present invention include all presently known IOP-lowering pharmaceuticals", including (without limitation) miotics, α and β adrenergic agonists, beta blockers, prostaglandins, carbonic anhydrase inhibitors. See DeSantis et al., paragraph [0023]. Brimonidine is listed among such compounds.

DeSantis does not disclose and provides no reason for the person of ordinary skill to specifically select an admantidine-based glutamate antagonist for use as an efficiency-enhancing component or in a combination therapy from among the exceedingly

large genus of possible combinations of "glutamate antagonists". See DeSantis at ¶[0023].

But even more importantly, DeSantis does not disclose, and provides no reason for a person of ordinary skill in the art to make, a single, conjugated molecule comprising any of the IOP-controlling compounds or glutamate antagonists disclosed therein.

Collins appears to be cited by the Examiner simply to show that conjugated pharmaceutical agents are known. Collins does not disclose ophthalmic compositions or diseases of the retina or posterior segment.

In the recent United States Supreme Court case *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. ___, ___ U.S.P.Q.2d___ (2007), Justice Kennedy affirmed that *Graham v. John Deere* continues to set forth the proper analytical test for obviousness. Pursuant to *Graham*, in an obviousness analysis, when "a person having ordinary skill in the prior art . . . would immediately see that the thing to do was what" the inventor did, the invention is obvious. *Graham*, 383 U.S. at 24, 148 U.S.P.Q. at 469 (emphasis added).

The *KSR* Court restated the *Graham* standard, stating that that when there are "a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known opinions within his or her technical grasp." *KSR*, 127 S. Ct. 1727, 1742 (2007).

Even more recently, the United States Court of Appeals for the Federal Circuit clarified that “[t]he passage above in *KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness.” *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, __ F.3d __, __ U.S.P.Q.2d __ (Fed. Cir. March 31, 2008) (slip op. 2007-1223 at 9) (emphasis added).

Chemical compositions were at issue in the *Ortho-McNeil* case. The court found that “the ordinarily skilled artisan would have to have some reason to select (among several unpredictable alternatives) the exact route” that provided the claimed composition. In finding the claimed compounds non-obvious, the *Ortho-McNeil* court concluded that the prior art did not provide “the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness.” *Id.* at 9-10.

Applying the law of obviousness to the present case, it can be immediately seen that the combination of DeSantis and Collins does not provide any reason for a person of ordinary skill in the art to make ophthalmic compositions containing the conjugate of the present claims, comprising a therapeutic agent and an amantidine moiety targeting the posterior segment of the eye.

Both the United States Supreme Court, in *KSR*, and the United States Court of Appeal for the Federal Circuit in *Ortho-McNeil* have recently opined on the insidious nature of hindsight. In *Ortho-McNeil*, the court held that a person of ordinary skill in the art would have to have some reason to

select the composition claimed from among several unpredictable alternatives. The court held that this was extremely unlikely since "the ordinary artisan in the field would have had to (at the time of the invention without any clue as to the potential utility of [the compound]) stop . . . and test it for properties" different from the purpose disclosed by the prior art. *Ortho-McNeil*, 2007-1223 at 9.

Here the properties disclosed by DeSantis (anterior segment-acting IOP lowering activity) is far different than the posterior segment-acting neuroprotective activity of the present compositions. Nothing in the combination of DeSantis and Collins even remotely suggests testing a conjugate containing a therapeutic component and an EEC for retinal neuroprotective activity or delivery of a topical composition to the retina.

Thus, respectfully, the situation is here as it was in the *Ortho-McNeil* case, in which a fact-finder " simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention . . . was obvious. Of course, this reasoning is always inappropriate for an obviousness test based on the language of Title 35 that requires the analysis to examine 'the subject matter as a whole' to ascertain if it 'would have been obvious at the time of the invention' ". *Id.* at 10 (emphasis added). Thus, "a flexible TSM [teaching, suggestion, motivation] test remains the primary guarantor against a non-statutory hindsight analysis" *Id.* at 11.

For this reason, the presently claimed invention is not *prima facie* obvious over DeSantis and Collins.

- 2) Even assuming *arguendo* that the present claims are *prima facie* obvious over the combination of DeSantis and Collins, secondary considerations conclusively rebut this presumption.

While the Applicants vehemently believe that the presently claimed invention is not *prima facie* obvious over the combination of DeSantis and Collins, even if the Board were to find that a *prima facie* case of obviousness were established, these references teach away from the invention. Moreover, the activity of the claimed composition constitutes surprising results in light of the combination of DeSantis and Collins. Thus, there are strong secondary considerations that effectively rebut any presumption that the presently claimed invention is obvious in light of DeSantis and Collins.

The combination of DeSantis and Collins actually teaches away from the present invention, since DeSantis is concerned with ocular hypertensive effects targeting the anterior segment of the eye and Collins does not disclose ocular therapeutics at all.

By contrast, as disclosed in the current specification, "the EECs of the present invention bind to the retinal epithelium. The binding of the EECs to the retinal epithelium may cause the TCs to become more bioavailable, in particular at or near the retinal epithelium." *Specification*, page 11, lines 8-12. The retinal epithelium is located in the posterior segment of the eye. Thus, the present conjugate serves to preferentially target the TC moiety of the topically applied conjugate to the posterior segment of the eye. Nothing in

either DeSantis or Collins suggests or motivates one of ordinary skill in the art to make such compositions.

The present invention, which targets therapeutic agents to the posterior segment of the eye, represents a significant advance in the treatment of conditions of the posterior segment, since it is well known by those of skill in the art that ophthalmic agents tend not to migrate well to the posterior segment when topically applied to the ocular surface. As stated in the specification, many TCs may not have the proper lipophilicity to penetrate the various layers of the eye to reach the retina. *Specification* at page 10, lines 35-38.

In their December 26, 2005 Reply, the present Applicants provided data showing that the presently described prodrug conjugates are selectively targeted to melanin, which is preferentially found in the retinal epithelium located in the posterior segment of the eye, as described in the specification. These data are now being resubmitted in the Declaration of Patrick M. Hughes, Ph.D., filed herewith pursuant to 37 C.F.R. §1.132, and both the December 26, 2005 Reply as well as the Hughes Declaration are hereby incorporated by reference herein.

As outlined by Dr. Hughes in his Declaration, such selective retinal targeting would not be useful or desired in the methods and disclosure of DeSantis, since ocular hypertension, with which DeSantis is largely concerned, is a condition of the anterior segment of the eye. It is therefore critical in the disclosure of DeSantis that the IOP-lowering agents remain in the anterior segment to lower IOP (for example by decreasing the rate of aqueous humor production in the

ciliary body or by increasing the rate of uveal aqueous humor outflow) and thus help to prevent mechanical "crushing" injury to the retina.

The presently claimed invention therefore functions in a completely different manner than the combination of glutamate receptor antagonists and IOP lowering agents cited by DeSantis. This difference in function would cause those familiar with DeSantis to discard the idea of making the conjugates of the present invention, since such conjugates would tend to migrate to the posterior segment, thereby defeating the purpose of the combinations disclosed by DeSantis.

Collins discloses the use of conjugates comprising an antibiotic and a vitamin B12 or intrinsic factor-binding agent targeting moiety for targeting of antibiotics to infected tissue. However, the combination of Collins and DeSantis does not lead to the compounds and compositions of the present invention. If there were any reason at all to consider conjugating the IOP lowering agents and glutamate antagonist agents of DeSantis based upon the disclosure of conjugates provided by Collins, the person of skill in the art would immediately dismiss this idea as failing to provide a solution to the problem addressed by DeSantis; delivering an IOP lowering agent to the anterior segment of the eye.

For this reason, the combination of DeSantis and Collins teach away from the present invention, which acts in a different and unexpected way. Even though Applicants do not believe that the prior art raises a *prima facie* case of obviousness, Applicants note that the United States Court of Appeals for the

Federal Circuit indicates that "an applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect", *In re Peterson*, 315 F.3d 1325, 1331, 65 USPQ2d 1379 (Fed. Cir. 2003). Applicants submit that the present rejection is a clear example of this.

In addition, DeSantis' disclosure of the treatment of glaucoma through the administration of combination of an IOP lowering agent and a glutamate receptor antagonist in no way suggests the conjugates of the presently claimed ophthalmic compositions.

To be effective, DeSantis' combinations require that upon topical administration the glutamate receptor antagonists be present within the posterior segment of the eye, where they may interact with retinal ganglion cells and optic nerve fibers to prevent damage associated with excitotoxicity. See DeSantis at ¶[0007]. At the same time, in order to be effective in the manner disclosed by DeSantis the IOP lowering agent must be present in the anterior segment of the eye (such as the uvea and the ciliary body) to reduce ocular hypertension and thus help prevent retinal damage due to mechanical, circulatory, and other poorly understood factors associated with high IOP.

In other words, as disclosed by DeSantis, the IOP lowering agent and a glutamate receptor antagonist must act in different compartments (the anterior and posterior chambers, respectively) in order to function.

In the present invention, the TC and EEC are and must be targeted to the same intraocular locus (the posterior segment) by virtue of being linked in a single molecule.

Like the present invention, Collins also discloses molecular conjugates. However, the person of ordinary skill in the art would not look for a way to accomplish the effect of DeSantis by creating a single molecule comprising a TC and an EEC.

Only the present invention recognizes that the therapeutic components of the composite disclosed therein may be effective when the therapeutic agent is delivered to the posterior, rather than the anterior segment of the eye, and provides a composition effective to enhance such delivery.

For these reasons, the invention is in condition for allowance.

b) Claims 24-26.

a) Did the examiner err by finding that the presently claimed ophthalmic compositions comprising molecular conjugates are obvious over DeSantis, which describes methods for treating conditions of the anterior segment of the eye with a combination of an IOP-lowering agent and a glutamate antagonist, and Collins, which discloses conjugates comprising antibiotic agents and a cobalamine.

1) The combination of DeSantis and Collins teach away from a conjugate-containing ophthalmic composition comprising an ophthalmically useful quinoxoline component and a covalently coupled adamantidine EEC moiety targeting the posterior segment of the eye which will deliver the conjugate

to a posterior portion of an eye upon topical delivery.

Applicants incorporate by reference the arguments made with respect to claims 1-6, 8, 9, 11, 12, and 14-16 above. In addition, Applicants have the following comments.

The invention of claim 24 is directed to an ophthalmic composition comprising a conjugate that includes an ophthalmically useful quinoxaline covalently linked to an EEC of a given structure, wherein the conjugate is targeted to the posterior segment of the eye upon topical delivery of the composition. Claim 25 is directed to a subgenus of quinoxalines, while claim 26 is directed to the specific quinoxaline brimonidine tartrate.

Certain ophthalmically effective quinoxoline components are useful to lower intraocular pressure. For example, DeSantis discloses that the quinoxaline compound brimonidine is a useful alpha 2 agonist IOP lowering agent. DeSantis is generally drawn to the topical application of a combination of a glutamate receptor antagonist and an IOP lowering agent for the treatment of elevated intraocular pressure.

However, as outlined in the argument above with respect to claims 1-6, 8, 9, 11, 12, and 14-16, the problem and solution disclosed by DeSantis teach away from the use of IOP agents targeted to the posterior segment of the eye. The primary ocular hypotensive mechanism of action of quinoxalines, including brimonidine, is the activation of the alpha 2 adrenoceptors in the ciliary body, thereby decreasing cyclic adenosine monophosphate(cAMP) levels and thus decreasing aqueous

humor production in the anterior chamber of the eye.

DeSantis' strategy of treating elevated IOP using a glutamate receptor antagonist and an IOP lowering agent depends upon efficient delivery of the IOP lowering agent to the anterior chamber of the eye. However, the present invention includes a conjugate compound that is specifically formulated to deliver the quinoxaline to the posterior chamber of the eye, where it may exert a neuroprotective activity. This activity is nowhere suggested in DeSantis or Collins, nor is the retinal epithelium targeting activity of the EEC of the present invention. This is indeed a surprising result, as explained above.

Collins discloses conjugates, but does not render the present invention obvious in light of DeSantis, since, unlike the present invention, Collins is not concerned with preferentially delivering compounds to the posterior segment of the eye.

Thus, the combination of DeSantis and Collins does not lead one of skill in the art to the present invention but rather directs such a person away from a composition that delivers the quinoxaline, including brimonidine, to the posterior segment rather than the anterior segment of the eye. Because of this, the combination of DeSantis and Collins do not render the invention of claims 24-26 obvious.

2) The combination of DeSantis and Collins provide no reason, or suggestion why a person of skill in the art would make the present invention comprising an ophthalmic composition comprising an ophthalmically useful quinoxoline component and a

covalently coupled admantidine EEC moiety targeting the posterior segment of the eye which will deliver the conjugate to a posterior portion of an eye upon topical delivery.

Applicants incorporate by reference the arguments made with respect to claims 1-6, 8, 9, 11, 12, 14-16 above. In addition, Applicants have the following comments.

Specific IOP lowering quinoxaline compounds are alpha 2 receptor agonists that are believed to act on the alpha 2 adrenoreceptors located in the ciliary body of the eye to reduced aqueous humor outflow, thereby decreasing IOP. The ciliary body is located in the anterior chamber of the eye.

The combination of DeSantis and Collins provide absolutely no reason for the person of ordinary skill in the art to make ophthalmic compositions comprising the presently disclosed conjugates. The teachings of DeSantis would not lead, even in light of the disclosure of antibiotic/vitamin B12 conjugates disclosed by Collins, the person of ordinary skill in the art to opt to make a topical ophthalmic composition comprising a quinoxaline - admanidine conjugate to target the posterior segment of the eye. This is particularly true when the targeting of retinal epithelial tissue by the admanidine moiety of the conjugate appear to defeat the object of DeSantis to provide IOP lowering activity (which is provided in the anterior segment ciliary body for the alpha 2 agonist quinoxalines) in the combination therapy it discloses.

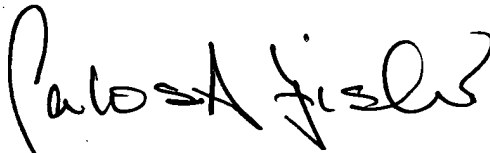
For these reasons, Applicant respectfully ask the Board to reverse the Examiner's contention that claims 24-26 are obvious in view of DeSantis and Collins.

CONCLUSION

For the foregoing reasons Applicants respectfully request that the Board affirm the patentability of the pending claims and permit these claims to proceed to issue.

Applicants have filed herewith either a check or deposit account authorization for payment of the fee associated with the filing of this Appeal Brief. If any other fee is due, Applicants hereby authorize the Commissioner to use Deposit Account 50-4004 for the payment of such fee.

Respectfully submitted,

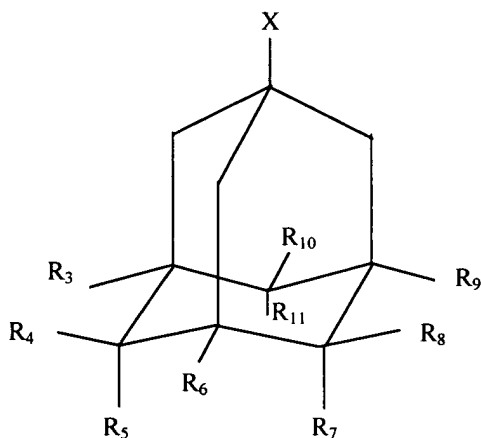
A handwritten signature in black ink, appearing to read "Carlos A. Fisher", written in a cursive style.

Carlos A. Fisher
Reg. No. 36,510
Attorney for Applicants

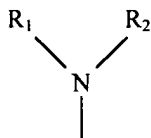
Stout, Uxa, Buyan & Mullins LLP
4 Venture
Suite 300
Irvine, California 92618
(949)-450-1750

CLAIM APPENDIX

1. (Previously presented) A topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate comprising an ophthalmically useful therapeutic component covalently coupled to an efficacy enhancing component effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye, the efficacy enhancing component having the formula A:



wherein X is



R1, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are independently an H, a C1-C10 hydrocarbon, or a linker.

2. (Previously presented) A composition of claim 1 wherein the therapeutic component and the efficacy enhancing component

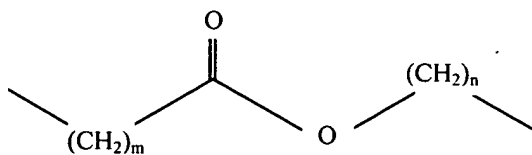
are directly joined by a covalent bond, and the carrier comprises a liquid.

3. (Previously presented) A composition of claim 1 wherein the therapeutic component and the efficacy enhancing component are joined by a linker.

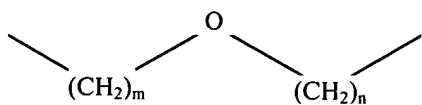
4. (Previously presented) A composition of claim 1 wherein R1 and R2 are Hs, and R3 is a linker.

5. (Previously presented) A composition of claim 1 wherein the efficacy enhancing component is a memantine.

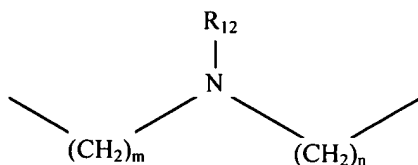
6. (Previously presented) A composition of claim 1 wherein the linker is selected from the group consisting of:



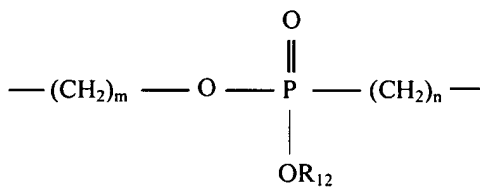
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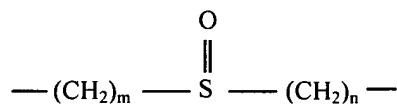
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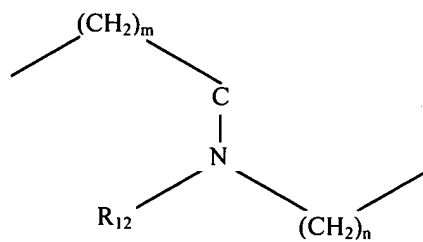
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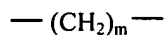
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Linker H

wherein R12 is an H or a C1-C10 hydrocarbon, m = 0 to 10, and n = 0 to 10.

7. (Withdrawn) A pharmaceutical conjugate of claim 1 wherein the therapeutic component is selected from the group consisting of NMDA antagonists, antibacterials, antihistamines, decongestants, antiinflammatories, antiparasitics, miotics, anticholinergics, adrenergics, antivirals, local anesthetics, antifungals, amoebicidals, trichomonocidals, analgesics, mydriatics, antiglaucoma drugs, carbonic anhydrase inhibitors, ophthalmic diagnostic agents, ophthalmic agents used as adjuvants in surgery, chelating agents, antineoplastics, antihypertensives, muscle relaxants, diagnostics, tyrosine kinase inhibitors and neuroprotectants.

8. (Previously presented) A composition of claim 1 wherein the therapeutic component is selected from the group consisting of quinoxaline, (2-imidazolyl-2-ylamino) quinoxaline, 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline, and mixtures thereof.

9. (Previously presented) A composition of claim 1 wherein the efficacy enhancing component comprises a memantine, and the conjugate further comprises a linker joining the therapeutic component and the memantine.

10. (Withdrawn) A pharmaceutical conjugate of claim 1 wherein the therapeutic component comprises a timolol and the efficacy enhancing component comprises a memantine, and the conjugate further comprises a linker joining the timolol and the memantine.

11. (Previously presented) A composition of claim 8 further comprising a memantine, and a linker joining the therapeutic component and the memantine.

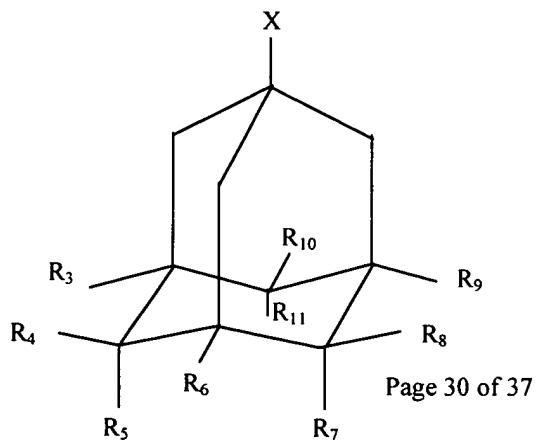
12. (Previously presented) A composition of claim 1 wherein the therapeutic component and the efficacy enhancing component disassociate under physiological conditions.

13. (Cancelled)

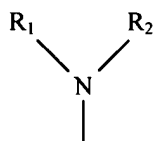
14. (Previously presented) A composition of claim 1 wherein the conjugate has an aqueous solubility, a partition coefficient and/or an affinity for melanin that is greater relative to a compound comprising the same therapeutic component which is not joined to an efficacy enhancing component.

15. (Previously presented) A composition of claim 1 wherein the conjugate is a salt.

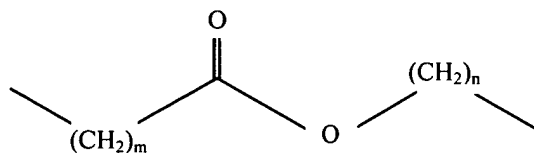
16. (Previously presented) A topical ophthalmic composition comprising a carrier and a pharmaceutical conjugate comprising an ophthalmically useful therapeutic component covalently coupled to an efficacy enhancing component effective in delivering the conjugate to a posterior portion of an eye of an individual when the composition is topically administered to the eye, the efficacy enhancing component having the formula A:



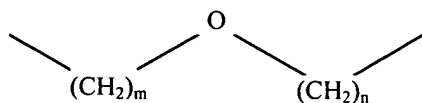
wherein X is



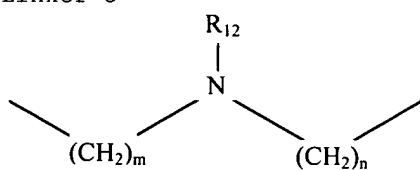
R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀ and R₁₁ are independently an H, a C₁-C₁₀ hydrocarbon, or a linker; the linker is selected from the group consisting of:



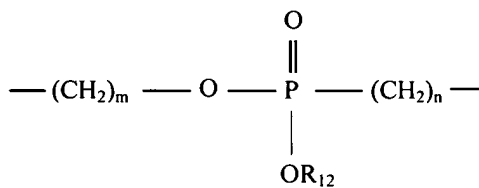
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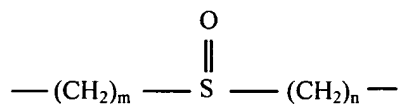
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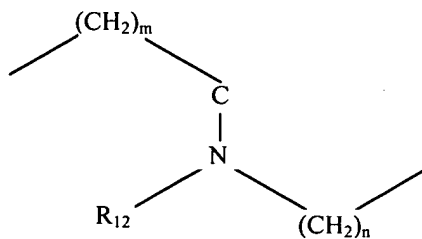
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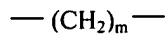
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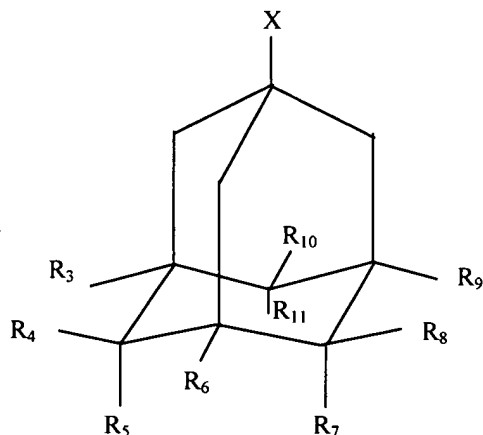


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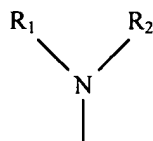
wherein R12 is an H or a C1-C10 hydrocarbon, m = 0 to 10, and n = 0 to 10.

17-23. (Cancelled)

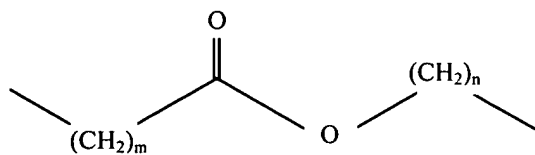
24. (Previously presented) An ophthalmic composition comprising a carrier and a pharmaceutical conjugate comprising an ophthalmically useful quinoxaline component-containing therapeutic component covalently coupled to an efficacy enhancing component effective in delivering the conjugate to a posterior segment of an eye of an individual when the composition is topically administered to the eye, the efficacy enhancing component having the formula A:



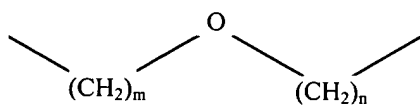
wherein X is



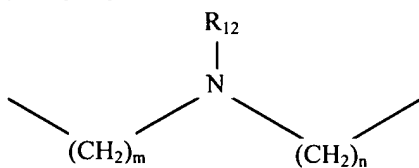
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10 and R11 are independently an H, a C1-C10 hydrocarbon, or a linker; the linker is selected from the group consisting of:



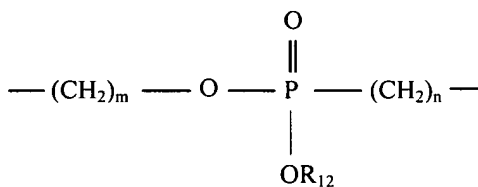
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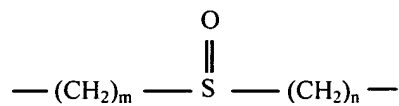
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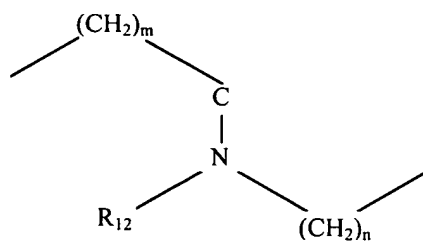
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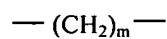
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wherein R12 is an H or a C1-C10 hydrocarbon, m = 0 to 10, and n = 0 to 10.

25. (Previously presented) The composition of claim 24 wherein the therapeutic component is selected from the group consisting of quinoxaline, (2-imidazolyl-2-ylamino) quinoxaline, 5-bromo-6-(2-imidazolyl-2-ylamino) quinoxaline, and mixtures thereof.

26. (Previously presented) The composition of claim 25 wherein the therapeutic component comprises brimonidine tartrate.

EVIDENCE APPENDIX

1. Declaration of Patrick M. Hughes, Ph.D.

RELATED PROCEEDINGS APPENDIX

None